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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,967	02/15/2002	William E. Rich	016866-005710US	1477

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EXAMINER	
CLOW, LORI A	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,967	RICH ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-20,24,25 and 31-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 18-20, 24, 25, and 31-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 20 December 2004, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-16, 18-20, 24, 25, and 31-54 are currently pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 54 recites "The method of claim 1, comprising the step of removing post-translational modifications of polypeptides prior to the fractionation of step (d)". Applicant points to paragraph [100] in support of this limitation. However, paragraph [100] does not include this particular limitation. Instead, paragraph [100] describes the technique of MALDI for fractionation of proteins, and not the removal of translational modifications prior to fractionation. *This is a new matter rejection.*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18-20, 24, 25, and 31-54 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for the reasons set forth in the previous Office Action and re-iterated below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to correlate gene expression and protein expression in a biological sample by obtaining a sample; generating a gene expression profile, thereby identifying an mRNA expressed in the sample; identifying a physio-chemical property of a polypeptide encoded by the mRNA; fractionating the polypeptide based on the physio-chemical property; and identifying the polypeptide encoded by

the mRNA from among the fractionated proteins, thereby correlating gene and protein expression.

For the reasons discussed below, this constitutes undue experimentation.

b) and c) The specification provides general examples of various gene expression profiling techniques which are well known in the art. For example at page 18, the specification states that the methods for examining gene expression include northern blots, dot blots, and PCR related techniques, and nucleic acid arrays. The specification then describes the various physio-chemical properties of amino acids and how they may be used to fractionate proteins for analysis, also techniques well known in the art. Finally the specification states that once the polypeptides are fractionated a next step is to identify a polypeptide from among the fractionated polypeptides that corresponds to the polypeptide encoded by the selected mRNA and somehow correlate this to gene expression.

However, there is nothing in the claims or in the specification that would guide one of skill in the art to practice this invention because it is not defined how one goes from the step of generating a gene expression profile of mRNA that is expressed to identifying a physio-chemical property of a polypeptide encoded by the mRNA and thereby correlating gene and protein expression in this step-by step way. How does one go from step (b) to step (c) without actually having the protein? How does one identify a physio-chemical property of the polypeptide encoded by the mRNA when all one has is the mRNA? No link has been established for doing so.

Secondly, how does one correlate gene expression with protein expression considering there is a diversity of proteins which can be generated from a single gene due to differential

splicing, for example (post-transcriptional changes)? There is not a strict linear relationship between genes and proteins.

The specification sites no working examples of the invention.

d) The invention is drawn to methods for correlating gene expression with protein expression.

e) and g) The prior art indicates that the activity state of a protein often depends on its modification state. i.e. post-translational modification, multiple initiation sites, abnormal termination etc. Furthermore, the expression of a gene may be the same in two situations. However the protein expression may not. For example, if the protein is phosphorylated or de-phosphorylated, this may indicate an active protein under one set of conditions or an inactive protein in the other. The prior art indicates that the number of genes in the human genome that are expressed easily reach 20,000. However, the actual numbers of proteins that are expressed reach far greater numbers. One of skill in the art would not know how to correlate gene expression levels with protein expression levels using the steps presented in the in the instant specification. (see Huber in Nature (2003) Vol. 4, pages 74-80 for a review of proteomics).

f) The skill of those in the art of molecular biology and protein chemistry is high.

The skilled practitioner would first turn to the instant specification for guidance to practice methods of correlating gene and protein expression. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows that would require substantial additional work and research. Finally, said practitioner would turn to trial and error experimentation to determine whether the mRNA could reliably be used to identify a

physio-chemical property of a protein, without the actual protein and that protein and gene expression could be correlated using this method. Such represents undue experimentation. No claims are allowed.

Response to Applicant's Arguments

Applicant argues that they have amended claim 1 in order to overcome the rejection pertaining to defining how one "goes from the step of generating a gene expression profile of mRNA that is expressed to identifying a physio-chemical property of an encoded polypeptide". Further, Applicant argues that "correlating" simply means that fractionated proteins may or may not contain a polypeptide encoded by the mRNA. Lastly, Applicant argues that the amendment adding "selecting one or more polypeptides from the fractionated polypeptides" overcomes the rejection.

However, these arguments are not persuasive. It still remains uncertain how one would identify a protein from an expressed mRNA, from amongst a set of fractionated polypeptides. Applicant has not addressed arguments in response to how one treats covalent modifications to the amino acid sequence, for instance. How does the method correlate anything if the fractionated sample does not contain a polypeptide encoded by the mRNA? How is this verified? As indicated above, the prior art teaches that correlation of gene expression with protein expression is not one to one, as there are far more proteins than expressed genes. There could be many proteins in the sample that contain the physio-chemical property of interest but not be related to the mRNA. The claims remain rejected under 112, 1st paragraph for lack of enablement.

Conclusion

Rejections under 35 USC 112, 1st paragraph-scope of enablement have been withdrawn in view of Applicant's response.

The objections to the specification and claims have been withdrawn in view of Applicant's response.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Ardin H. Marschel 4/3/05
ARDIN H. MARSCHEL
PRIMARY EXAMINER

March 30, 2005
Lori A. Clow, Ph.D.
Art Unit 1631
Lori A Clow